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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/162,648	09/29/1998	JOHN C. HISERODT		9087

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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	25

DATE MAILED: 12/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/162,648	John C. Hiserodt
Examiner	**Art Unit**
Shin-Lin Chen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 7, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-14, 16, 18-20, and 22-31* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-14, 16, 18-20, and 22-31* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment filed 10-9-02 has been entered. Claims 15, 17 and 21 have been canceled. Claims 23-31 have been added. Claims 1-14, 16, 18-20 and 22-31 are pending and under consideration.

Claim Objection

1. Applicant is advised that should claim 10 be found allowable, claim 16 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MEP. § 706.03(k).

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 10 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "removing any residual tumor at or around the site of the second cell population at a time subsequent to when the second cell population was implanted" in claim 10

and 16 is vague and renders the claims indefinite. Claim 1 specifies the tumor cells are left at the site before administering the second cell population. It is unclear how the tumor cells are left at the site and further being removed from the site of second cell population. If the tumor cells are removed after the second cell population was added to the tumor site, it is unclear how to remove the tumor cells only but to leave the second cell population at the tumor site.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-10, 12-14, 16, 19, 20 and 22-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Granger (US Patent 5,837,233) in view of Hiserodt et al., 1998, WO 98/16238.

Claims 1-10, 12-14, 16, 19 and 22 are directed to a method for treating cancer, such as melanoma, pancreatic cancer, liver cancer, breast cancer etc., in a human patient by implanting at or around the site of a tumor in the patient a first cell population containing alloactivated lymphocytes that are allogeneic to leukocytes such that the tumor cells are left at the site and implanting a second cell population containing alloactivated lymphocytes, and the first and second cell population is administered at an interval of at least 3 days, wherein said treatment induces anti-cancer immune response by the patient against tumor, and a pharmaceutical

composition comprising alloactivated lymphocytes packaged with information for the treatment of the patient. Claims 3 and 4 specify the response is inflammatory and immunological response, respectively. Claim 5 specifies the alloactivated lymphocytes in at least one of the cell population are alloactivated against leukocytes of the human patient. Claims 7 and 8 specify the interval is between one and eight weeks or two and twelve months. Claims 20 and 23-31 are directed to an improvement in the method of treating a human patient having a tumor, such as melanoma, pancreatic cancer, liver cancer, breast cancer etc., by implanting at or around the site of a solid tumor a cell population comprising alloactivated lymphocytes that are allogeneic to the patient to generate a therapeutic response against tumor growth and the improvement comprises implanting at or around the solid tumor site a second cell population containing alloactivated lymphocytes to the patient between 1 and 8 weeks after the implanting of first cell population. Claims 24 and 25 specify the response is inflammatory and immunological response, respectively.

Granger teaches a method for treating cancer, such as melanoma, pancreatic, liver, colon, prostate and breast cancer, in a human patient comprising implanting at or around the site of a tumor a cell population of about $2x10^9$-$6x10^9$ cells and comprising alloactivated human donor lymphocytes produced by coculturing said lymphocytes ex vivo with leucocytes from said patient at a ratio of 10:1 to 20:1 donor: patient cell ratio, for at least 48 hours, and preferably 1-5 days (claim 37, column 7). Treatment results in the patient generating a therapeutic or immunologic response against tumor growth and transplanted lymphocytes up to 74 weeks post implant

(column 4, 11-14). Granger also teaches the use of a pharmaceutical composition comprising a sterile vial containing a unit dosage of mixed lymphocyte culture (a mixture of live alloactivated donor and patient lymphocytes) and bearing a label which set forth information concerning the pharmaceutical use of the composition in treating a tumor in a human (column 6). In addition, Granger teaches implanting the alloactivated lymphocytes to the proximity of a surgically debulked tumor or an inoperable tumor, i.e. the tumor has not been removed (column 3), and teaches "In accordance with conventional prudent formulating practices, a dosage near the lower end of the useful range may be employed initially and the dosage increased or decreased as indicated from the observed response, as in the routine procedure of the physician" (column 5-6).

Granger does not teach the intervals between the first and second cell populations is at least 3 days, between one and eight weeks, or between two and twelve months.

Hiserodt teaches a method for stimulating an anti-tumor immunological response or treating a neoplastic disease, such as melanoma, pancreatic cancer, liver cancer, colon cancer, prostate cancer, and breast cancer, in a human comprising mixing *ex vivo* a first cell population comprising tumor cells, and a second cell population comprising lymphocytes allogeneic to the lymphocytes, to produce a cell mixture, and administering an effective amount of the cell mixture to the human (e.g. page 58-59). Hiserodt teaches alloactivated allogeneic lymphocytes can be administered into a solid tumor in the human or at or around a site where a solid tumor or a portion thereby has been removed (e.g. p. 58). Hiserodt also teaches that additional doses may be given, such as on a monthly or weekly basis, until the desired effect is achieved (e.g. page 27).

It would have been obvious for one of ordinary skill at the time of the invention to administer the first and second cell populations at an interval of at least 3 days , between 1 and 8 weeks, or between two and twelve months because Granger teaches conventional prudent formulating practices with more than one doses in treating tumors and Hiserodt teaches that additional doses may be given, such as on a monthly or weekly basis, until the desired effect is achieved. Further, different interval times of administration are routine optimization of variables for obtaining better effects of the allogeneic CTLs and would be obvious for one of ordinary skill.

One ordinary skill at the time the invention was made would have been motivated to do so in order to generate a therapeutic or immunologic response against tumor growth as taught by Granger and stimulate an anti-tumor immunological response or treat a neoplastic disease, such as melanoma, pancreatic cancer, liver cancer, and breast cancer, in a human as taught by Hiserodt with reasonable expectation of success.

Applicant argues that leaving the tumor cells at the tumor site at the time of first injection renders the claimed invention non-obvious and cites example 6. Applicant further argues that it is counter-intuitive to leave a tumor cells in a patient when tumor is sufficiently accessible to be removed and Granger teaches removing the tumor (amendment, p. 7). This is not found persuasive because of the reasons set forth above under 103(a) rejection and that the claims do not specify the tumor has to be removed and at the same time leave some tumor cells behind at tumor site. The claims encompass injecting the first cell population into a tumor. As discussed

above, Granger does teach injecting the alloactivated lymphocytes to **inoperable tumor** and renders the claimed invention obvious.

Applicant argues that Claim 23 specifies the alloactivated cells have to be administered one to eight weeks after the first implant and in Figure 2 of Granger patent, there is no evidence for upward sloping volumes in any of the patients treated until outside the eight week window. Therefore, there is no motivation to administer a second implant before eight weeks (amendment, p. 8). This is not found persuasive because of the reasons set forth above under 103(a) rejection. Hiserodt teaches that additional doses may be given, such as on a monthly or weekly basis, until the desired effect is achieved. It was common practice at the time of the inveniton to have multiple administrations to ensure better results of a treatment. In Figure 2 of Granger patent, the tumor volume of 4 patients (Schmidt, Howland, Benge, and Reddy) remain the same after about 3-4 weeks and the tumor volume of Lavender in fact starts to increase after about 3-4 weeks. Thus, one of ordinary skill in the art would have been motivated to administer another dose of alloactivated lymphocytes in order to further reduce the tumor volume of the patients. Therefore, it would have been obvious for one of ordinary skill at the time of the invention to administer a second dose of alloactivated lymphocytes to tumor site of a patient in an appropriate time interval, such as between 1 and 8 weeks.

6. Claims 11 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Granger (US Patent 5,837,233) in view of Hiserodt et al., 1998, WO 98/16238 as applied to claims 1-10, 12-14, 16, 19, 20 and 22-31 above, and further in view of Haugland (1992) and Jung (1990).

Claims 11 and 18 further comprises the process wherein donor lymphocytes are alloactivated by culturing ex vivo with stimulator leukocytes and harvested at about the time of initial allocactivation, measurable by acridine orange and CD69 assay.

Haugland teaches that fluorescence methods provide accurate, reproducible determination of cellular viability and proliferation, and acridine orange is a fluorescent dye utilized for assessing cell function, such as metabolic process (p. 172, 173).

Jung teaches that CD69 is an antigen on human lymphocytes expressed during the early stages of cell activation (abstract).

It would have been obvious for one of ordinary skill at the time of the invention to use acridine orange or CD69 assays because they were routine in the art of studying cellular metabolic processes (Haugland, p. 173) and that CD69 expression is specific to early stage activated lymphocytes. One of ordinary skill at the time the invention was made would have been motivated to do so in order to determine the point of initial alloactivation of the lymphocytes according to the teachings of Granger, Hiserodt, Haugland and Jung with reasonable expectation of success.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.